REMARKS

The Examiner's attention to this Application is greatly appreciated. Please note that citations to the Specification of the instant Application in this Response refer to the published Application. Please note also that the compound 1-amino-3-(n,n-dimethylamino)-propylidene-1,1-bisphosphonic acid is referred to as "NH_2-OPD" in this Response.

I. STATUS OF THE CLAIMS

Claims 1-31 are cancelled. Claims 47-53, and 55-57 are withdrawn. Claims 32-62 are pending. Claims 34, 38 and 46 are currently cancelled. Claims 32, 39-41, 44, 45 and 54 are currently amended. Claims 60-62 are new.

Applicants do not concede in this Application that the amended claims are not patentable, as the present claim amendments are only for facilitating expeditious prosecution of the allowable subject matter noted by the Examiner. Applicants respectfully reserve the right to pursue these and other claims in one or more continuation or divisional patent applications.

II. AMENDMENTS

Claim 32 is currently amended as shown below:

> A method for maintaining a healthy bone structure, said method comprising administering to a patient <u>without an osteopathy</u> a medicament comprising a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates.

The element of a patient without an osteopathy is disclosed in paragraph 0038 of the published Application. The Applicants submit that the amendment does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 39 is amended as shown below:

A method according to claim 32 ~~38~~, wherein the osteopathy is selected from the group comprising osteoporosis, Paget's disease, arthritis, peridental osteopenia, adolescent scoliosis, fracture, disuse osteopenia, post-transplant osteopenia, hyper-parathyoidism-associated, metabolic bone disease, osteopenia of prematurity, ~~and~~ ossification disorder, or a combination thereof.

Claim 39 now depends on Claim 32, wherein it previously depended on Claim 38. The Markush group now includes "a combination" of the elements in the group. The Applicants submit that the amendment does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 40 is amended as shown below:

A method for treatment of a patient who has ~~recently~~ undergone treatment with corticosteroids, said method comprising administering to said patient who has ~~recently~~ undergone treatment with corticosteroids a medicament comprising a bone-health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates.

The word "recently" has been deleted. Treatment of patients having undergone treatment with corticosteroids is disclosed in the Specification, at paragraphs 0017, 0034, and 0039 of the published Application. The Applicants submit that the amendment does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 41 is amended as shown below:

A method for post-treatment of osteopathies wherein an anti-resorptive activity is not desired, said method comprising administering to a patient in need thereof a medicament containing a bone-health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates, wherein said amount is selected from the group consisting of: 0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration.

The limitation of "0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration" has been added. This range of amounts is disclosed in the Specification at paragraphs 0035, 0046 and 0047 of the published Application. The Applicants submit that the

amendment does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 44 is amended as shown below:

A method as in claim 42, wherein said amount is selected from the group consisting of: 0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration ~~after the administration of medicament to the patient the 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, or any of its soluble salts or any of its hydrates are present at extracellular concentrations in a range of between 10^{-6}M and 10^{-10}M~~.

Matter has been deleted from the claim. The limitation of "0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration" has been added. This range of amounts is disclosed in the Specification at paragraphs 0035, 0046 and 0047 of the published Application. The Applicants submit that the amendment does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 45 is amended as shown below:

A method according to claim 44, wherein said amount is selected from the group consisting of: 12.5-75 mg per oral administration, and 2.5-15 mg per parenteral administration ~~1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, or any of its soluble salts or any of its hydrates, are present at extracellular concentrations in a range of between 10^{-7}M and 10^{-9}M~~.

Matter has been deleted from the claim. The limitation of "12.5-75 mg per oral administration, and 2.5-15 mg per parenteral administration" has been added. This range of amounts is disclosed in the Specification in paragraphs 0046 and 0047 of the published Application. The Applicants submit that the amendment does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 54 is amended as shown below:

[[A]] The method of Claim 32 ~~for prevention or treatment of a bone disorder~~, said medicament further comprising ~~method comprising administering to a patient a medication comprising (a) a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of~~

~~its hydrates, and (b)~~ at least one substance selected from the group consisting of calcium salts, calcium citrate, calcium carbonate, other amino-substituted bisphosphonates, pharmaceutically active fluorine-containing salts, vitamins of the D-Group and their metabolites, cholecalciferol, calcifediol, calcitriol, ergocalciferol, PTH, anabolic hormones, estrogens, substances with estrogenic activity on the bone, progestogens, androgens, growth hormones, peptides with growth hormone activity, selective modulators of the estrogenic receptor, and raloxifene.

Claim 54 has been amended into dependent form. The Applicants submit that the amendment does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 60 is new. Claim 60 recites:

A method for treatment of a bone disorder, said method comprising administering to a patient a medication comprising:
(a) a bone-health promoting effective amount of 1-amino-3-(N,N-dimethylamino) – propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates, and

(b) at least one substance selected from the group consisting of calcium salts, calcium citrate, calcium carbonate, other amino-substituted bisphosphonates, pharmaceutically active fluorine-containing salts, vitamins of the D-Group and their metabolites, cholecalciferol, calcifediol, calcitriol, ergocalciferol, PTH, anabolic hormones, estrogens, substances with estrogenic activity on the bone, progestogens, androgens, growth hormones, peptides with growth hormone activity, selective modulators of the estrogenic receptor, and raloxifene.

Claim 60 is identical to Claim 54 prior to amendment, but whereas Claim 54 is directed to a method of treatment or prevention, Claim 60 is directed only to a method of treatment. The Applicants submit that the new claim does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 61 is new. Claim 61 recites:

The method of claim 60, wherein said amount is selected from the group consisting of: 0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration.

The limitation of "0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration" is disclosed in the Specification at paragraphs 0035, 0046 and 0047 of the

published Application. The Applicants submit that the new claim does not constitute new matter, and respectfully request the Examiner enter the amendment.

Claim 62 is new. Claim 62 recites:

> A method according to claim 60, wherein the bone disorder is selected from the group comprising osteoporosis, Paget's disease, arthritis, peridental osteopenia, adolescent scoliosis, fracture, disuse osteopenia, post-transplant osteopenia, hyper-parathyoidism-associated, metabolic bone disease, osteopenia of prematurity, and ossification disorder, or a combination thereof.

The disorders in the Markush group are disclosed in the Specification at paragraphs 0041 and 0043 of the published Application.

III. REJECTIONS OF THE CLAIMS

A. NEW MATTER REJECTION OF CLAIM 38, 39 AND 54

On pages 2-5 of the Office Action the Examiner rejected Claims 32-46, 54, and 58-59 under 35 U.S.C. §112 as not supported by the specification. The Examiner wrote:

> Applicant's amendment with respect to claim 32 herein has been fully considered, but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for applicants' claim a composition comprising a "medicament comprising a bone health promoting effective amount of [NH_2-OPD]". The specification as filed provides support for a "bone-health promoting amounts of a medicament." The claims herein are directed to a "bone health promoting effective amount of [NH_2-OPD]". The scope of a bone health promoting medicament comprising said compound is different from the bone health promoting effective amount of said compound as claimed herein.

The Office Action cites the same logic to reject as new matter "a medicament comprising an osteopathy preventing effective amount of [NH_2-OPD]" and "a medicament comprising a bone health promoting effective amount of [NH_2-OPD]." Applicants respectfully traverse.

Applicants submit that a person having ordinary skill in the art of pharmacology ("a skilled artisan") understands that any pharmacologically active substance is only therapeutically effective in certain amounts. Too little of the drug will produce no beneficial effect, and too

much of the drug will have a toxic effect. This is described as "a fundamental hypothesis of pharmacology" by one popular treatise:

> Figure 3-1 illustrates a fundamental hypothesis of pharmacology, namely, that a relationship exists between a beneficial or toxic effect of a drug and the concentration of the drug. This hypothesis has been documented for many drugs, as indicated by the Effective Concentrations and Toxic Concentrations columns in Table 3-1. The apparent lack of such a relationship in some drugs does not weaken the basic hypothesis but points to the need to consider the time course of concentration at the actual site of pharmacologic effect (see below).

N. Holford (2001) "Pharmacokinetics & pharmacodynamics: Rational dosing & the time course of drug action" page 35, chapter in B. G. Katzung (2001) *Basic and Clinical Pharmacology* Lange Medical Books/McGraw-Hill, New York. Applicants submit that a skilled artisan will understand from the Specification that the disclosed beneficial effects of NH_2-OPD will only occur at certain effective amounts.

The Specification teaches that administration of NH_2-OPD is effective for the purposes of maintenance of a healthy bone structure, the prevention of osteopathies, the treatment of patients who have recently undergone treatment with corticosteroids, the post-treatment of osteopathies where an anti-resorptive activity is not desired, and the treatment of children having an osteopathy at paragraphs 0035 and 0036:

> [0034] The present invention also discloses a method for the selective modulation of osteoblasts and/or for the maintenance of a healthy bone structure and/or for the prevention of osteopathies in healthy patients and/or for the treatment of patients who have recently undergone treatment with corticosteroids, and/or for post-treatment of osteopathies where an anti-resorptive activity is not desired, and/or for the treatment of children having an osteopathy and/or for the stimulation of those signaling cascades and reaction mechanisms mediating the action of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid or any of its soluble salts or any of its hydrates, which can be blocked by Ca.sup.2+-channel blockers, and/or for the mobilization of Ca.sup.2+ ions from IP.sub.3-sensitive stores, comprising:
>
> [0035] administering 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphos- phonic acid or any of its soluble salts or any of its hydrates alone or in combination with a pharmaceutical carrier to a patient, the 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-

> bisphosphonic acid or any of its soluble salts or any of its hydrates being administered in doses of 0.1 to 1000 mg/oral application or 0.02 to 200 mg/parenteral application.

Applicants point out that this passage does not merely suggest that a medicament is effective to treat and prevent these conditions, in which NH_2-OPD is one component of the medicament. The cited passage teaches that the administration of NH_2-OPD itself (in combination with a carrier) treats and prevents the listed conditions. It is then a matter of basic pharmacology that NH_2-OPD only exerts beneficial effects at certain effective amounts.

In light of the evidence and arguments presented above, Applicants respectfully request the Examiner reconsider and withdraw the rejection and allow the claims.

B. INDEFINITENESS REJECTION OF CLAIM 40

On pages 4-5 of the Office Action the Examiner rejected Claim 40 as indefinite, arguing "The term is not clearly defined the specification, and one of skill in the art will not readily recognize which time duration is encompassed by the term 'recently.'" Applicants take no position on the correctness of the rejection. For the sole purpose of facilitating the prosecution of this Application Claim 40 is herein amended to omit the term "recently." Applicants submit the rejection is now moot. In light of the amendment and arguments presented above, Applicants respectfully request the Examiner reconsider and withdraw the rejection and allow the claims.

C. ENABLEMENT REJECTION OF CLAIMS 38, 39 AND 54

On pages 5-12 of the Office Action the Examiner rejected Claims 38, 39 and 54 under 35 U.S.C. §112 as non-enabled by the Specification, arguing "the specification, while being enabling for the treatment of bone disorders, does not reasonably provide enablement for the prevention of bone disorders or osteopathies as claimed." Applicants traverse, and further submit the rejection is moot in light of the current amendments.

Applicants re-allege and incorporate herein the arguments and evidence submitted in response to the Office Action of November 28, 2006, that the Examiner has adopted an improper definition of "prevention," that the current Office Action adopts the wrong standard for enablement under 35 U.S.C. §112, and that the Specification fully enables the claims.

Additionally, Applicants submit the rejection is moot in light of the instant amendments. Claim 38 is cancelled. Claim 39 no longer depends on Claim 38, and now claims "a method of maintaining a healthy bone structure" by virtue of its dependence on Claim 32. Claim 54 is amended to delete the preamble language of "prevention," and now claims "a method of maintaining a healthy bone structure" by virtue of its dependence on Claim 32.

In light of the amendments and arguments submitted above, Applicants respectfully request the Examiner reconsider and withdraw the rejection and allow the claims.

D. INDEFINITENESS REJECTION OF CLAIMS 44-46

On pages 12-13 of the Office Action, Claims 44-46 were rejected under 35 U.S.C. §112 as indefinite. The Examiner argues

> Claims 44-46 recites "after the administration to the patient — the [NH_2-OPD], or any of its soluble salts or any of its hydrates are present at extra cellular concentration in a range of between 10^6M and 10^{10}M" renders the claim indefinite. It is not clear how much of the [NH_2-OPD] needs to be administered to a patient to achieve such extra cellular concentration. As such, one of ordinary skill in the art will not be apprised of the metes and bounds of claimed invention.

Applicants take no position on the correctness or incorrectness of the Examiner's rejection. Applicants submit the rejection is moot in light of the current amendments to Claims 44-46. Claim 46 is cancelled. Claims 44 and 45 are amended to no longer include the limitations based on extracellular molarity of NH_2-OPD, but rather include limitations of amounts administered to patients.

In light of the amendments and arguments presented above, Applicants respectfully request the Examiner reconsider and withdraw the rejection and allow the claims.

E. ANTICIPATION REJECTION OF CLAIMS 32, 35, 41 AND 54

On pages 13-18 the Examiner rejected Claims 32, 35, 41 and 54 under 35 U.S.C. §102(b) as anticipated by WO 97/02827 to Van Beek et al. ("Van Beek"). Applicants respectfully traverse.

Applicants re-allege and incorporate herein the arguments presented in response to the Office Action of November 28, 2006. Applicants respectfully submit that the Examiner misunderstands the disclosure of Van Beek, and that Van Beek only teaches the usefulness of NH_2-OPD as a biologically-active carrier in medicaments directed to the treatment of osteopathy, and does not teach that NH_2-OPD itself is active in the treatment of osteopathy.

Applicants further submit that Van Beek does not anticipate Claims 32, 35, 41 and 54 because Van Beek does not teach every element of the rejected claims. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001) (claim to a system for setting a computer clock to an offset time to address the Year 2000 (Y2K) problem, applicable to records with year date data in "at least one of two-digit, three-digit, or four-digit" representations, was held anticipated by a system that offsets year dates in only two-digit formats). See also MPEP § 2131.02. "The identical invention must be shown in as complete detail as is contained in

the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Claims 35 and 54 as currently amended depend on Claim 32. Claim 32 recites:

> A method for maintaining a healthy bone structure, said method comprising administering to a patient without an osteopathy a medicament comprising a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates.

Applicants point out that Van Beek does not teach the administration of NH_2-OPD to a patient without an osteopathy or the administration of a bone-health promoting effective amount of NH_2-OPD. Van Beek teaches the administration of medicaments comprising NH_2-OPD to patients suffering from various osteopathies, and not to healthy patients without osteopathies, as claimed. Therefore Van Beek does not anticipate Claim 32 and its dependent Claims 35 and 54.

The Examiner states on page 17 of the Office Action that "As noted the disclosed ranges in Figures 1-3 acid in binding bone mineral, inhibition of calcium incorporation and crystal growth are considered to fall in the claimed range herein, 'bone health promoting effective amount.'" Applicants respectfully point out that Figures 1-3 of Van Beek do not teach amounts of a medicament to be administered, but rather extracellular concentrations used in *in vitro* tissue culture studies. Van Beek does not explicitly or inherently teach "a bone health promoting effective amount" of NH_2-OPD as claimed. Therefore Van Beek does not anticipate Claim 32 and its dependent Claims 35 and 54.

Claim 41 recites:

> A method for post-treatment of osteopathies wherein an anti-resorptive activity is not desired, said method comprising administering to a patient in need thereof a medicament containing a bone-health promoting effective amount of 1-amino-3-(N,N-

dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates, wherein said amount is selected from the group consisting of: 0.1-1000 mg per oral administration, and 0.02-200 mg per parenteral administration.

Applicants submit that Van Beek does not teach administration of an amount of NH_2-OPD of either 0.1-1000 mg per administration or 0.02-200 mg per administration. As Van Beek does not teach every element of the claim, Van Beek does not anticipate the claim.

Applicants submit that in light of the amendments and arguments presented above, Van Beek fails to anticipate Claim 32, 35, 41 and 54. Applicants respectfully request the Examiner reconsider the rejection, withdraw the rejection, and allow the claims.

F. OBVIOUSNESS REJECTION OF CLAIMS 33, 34, 36-40, 42-46, 58 AND 59

On pages 18-23 of the Office Action, the Examiner rejected Claims 33, 34, 36-40, 42-46, 58 and 59 under 35 U.S.C. §103 as obvious over Van Beek in combination with Brumsen (*Reviews in Molecular Medicine*, 76(4), 1997, pp. 266-283). Applicants respectfully traverse, as there was no motivation to combine the references for the purposes of the claimed methods.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or

motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006) (discussing rationale underlying the motivation-suggestion-teaching requirement as a guard against using hindsight in an obviousness analysis). The teaching, suggestion, or motivation must be found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also In re Lee, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34 (Fed. Cir. 2002) (discussing the importance of relying on objective evidence and making specific factual findings with respect to the motivation to combine references); *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

To understand why there was no motivation to combine Brumsen with Van Beek, it is helpful to briefly review the principles and mechanisms underlying the treatment and prevention of bone disorders by bisphosphonates. Concentration of mineral in bone is partially controlled by the activities of two classes of cell: osteoclast cells and osteoblast cells. Osteoblast cells function in the formation of bone. Osteoclast cells function in the destruction or "resorption" of bone. In healthy persons there is a balance between the activity of osteoclast cells and osteoblast cells that maintains a sufficient level of bone strength while preventing the formation of unhealthy "overgrown" bone structures.

Many widespread bone diseases, including osteoporosis, are the result of resorptive activity by the osteoclast cells that exceeds the bone formation activity of the osteoblast cells. As a result the mineral concentration in the bone decreases, compromising the bone's strength.

Because high resorptive activity in the osteoclast causes bone disease, methods of treating and preventing bone disease have focused on substances that reduce this activity in the osteoclast. Such substances are said to have "anti-resoprtive" properties. Bisphosphonates as a class are known to have high anti-resorptive activity. As a result of the anti-resorptive activity of most bisphosphonates, administration of anti-resorptive bisphosphonates leads to an increase in bone mineral density.

However, among the bisphosphonates it is known that NH_2-OPD lacks anti-resorptive properties. This can be seen in Figure 3 of Van Beek, on page 7/9 of the drawings. Whereas olpadronate completely inhibits calcium release at about 10^{-5} M, NH_2-OPD does not significantly reduce calcium release at any concentration.

Because NH_2-OPD lacks anti-resorptive activity, and because it is the anti-resorptive activity of bisphosphonates that was previously believed to be useful in treatment and prevention of bone disease, it was not obvious to use NH_2-OPD for the same purposes as olpadronate. Thus, the Examiner's conclusion on page 20 is erroneous:

> One of ordinary skill in the art would have reasonably expected that the use of 1-amino-3-(N, N-dimethylamino)-propylidene-1,1-bisphosphonic acid as claimed herein would be successful because Beek et.al. showed in comparison with olpadronate, the compound of the instant application has similar or better effects.

In fact, one of ordinary skill in the art would have concluded exactly the opposite. Without the anti-resorptive activity that is the basis of olpadronate's therapeutic value, one of ordinary skill in the art would have considered NH_2-OPD to be useless in the treatment of bone diseases such as osteoporosis, for which anti-resorptive activity is desirable. For the same reason, Van Beek concluded that NH_2-OPD would be useful as a carrier for anti-resorptive bisphosphonates, or as a treatment for calcification disorders for which anti-resorptive activity is not desirable (generally calcification disorders of the soft tissues, such as those cataloged by Van Beek on page 3).

Applicants submit that Van Beek's teaching that NH_2-OPD has no anti-resorptive activity teaches away from using NH_2-OPD for the same purposes as olpadronate that are taught by Brumsen. Brumsen is exclusively concerned with the treatment of osteoporosis. Osteoporosis was known as a disease that is treated and prevented by substances with anti-resorptive activity. Brumsen on page 1 explicitly recognized the value of anti-resorptive therapeutic agents to treat osteoporosis:

> Bisphosphonates, synthetic compounds that suppress bone resorption and reduce bone turnover, are effective in the treatment of patients with post-menopausal osteoporosis and have been shown to increase bone mass and reduce significantly the frequency of new vertebral fractures in controlled studies.

Brumsen on page 2 wrote that olpadronate was chosen for the study particularly because of its high anti-resorptive activity: "We used this particular class of bisphosphonates because their effective anti-resorptive concentrations are considerably lower than those inducing toxicity at the bone tissue level, making them more suitable for treating young patients than the first developed bisphosphonate, etidronate (1-hydroxyethylidene-1,1-bisphosphonate), which has a narrower therapeutic margin."

There is ample teaching in both Brumsen and Van Beek that anti-resorptive activity is critical to the treatment of bone disease by bisphosphonate. Prior to the instant invention, it was not known that NH_2-OPD exerts an effect on the osteoblast cells, and so exerts an effect on bone mineral density that is independent of anti-resorptive activity.

The ability of NH_2-OPD to stimulate osteoblast activity was not taught by the prior art. It was previously known that bisphosphonates have anti-catabolic effects on bone. However the anabolic effects on bone of NH_2-OPD were unexpected. The references cited by the Examiner assume the classic models of studies with bisphosphonates based on bone resorption. Therefore, they do not render obvious an anabolic mechanism on the bone-forming cells. The knowledge

that NH_2-OPD reduces calcification in soft tissue does not render obvious its application to increase calcification in bone. Up to now, it was known only the antiresorptive properties of bisphosphonates; the claimed invention employs anabolic properties, specifically for one compound that completely lacks the antiresorptive effect. NH_2-OPD, in contrast to other bisphosphonates, lacks antiresorptive effects; due to its bone affinity it is used as a carrier for other substances to the bone. Nowhere in the cited references is it suggested that the NH_2-OPD would have any anabolic effects.

However; the NH_2-OPD has surprisingly shown anabolic effects on osteoblast cells and for the first time a bisphosphonate compound with this effect is being described. The effects of antiresorptive bisphosphonates cannot be extrapolated to those of the NH_2-OPD. NH_2-OPD is useful when antiresorptive properties are not desired. For this reason, NH_2-OPD may be preferred over other bisphosphonates in treating children and corticosteroid patients.

In light of the arguments and amendments above, Applicants respectfully request the Examiner reconsider the rejection, withdraw the rejection, and allow the claims.

CONCLUDING REMARKS

For the reasons stated above, the Applicants submit that the claims are patentably distinct from the prior art. The Applicants submit that all claims are in condition for allowance. As such, the Applicants respectfully request that all rejections be withdrawn, all claims allowed, and the Application passed to issue.

The Applicants believe this Response and Amendment to be filed timely. The Commissioner for Patents is hereby authorized to charge the RCE fee under 37 C.F.R. §1.17(e), any amount due for retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

The Applicants are grateful for the Examiner's consideration of this matter. In light of the remarks above, the Applicants respectfully request the Amendments be entered, all rejections be withdrawn, and all claims be allowed. If the Examiner still has concerns as to the allowability of any claims, he is urged to telephonically contact the undersigned at the number below.

Respectfully submitted,

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Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action

3

Nicholas H.G. Holford, MB, ChB, FRACP

The goal of therapeutics is to achieve a desired beneficial effect with minimal adverse effects. When a medicine has been selected for a patient, the clinician must determine the dose that most closely achieves this goal. A rational approach to this objective combines the principles of pharmacokinetics with pharmacodynamics to clarify the dose-effect relationship (Figure 3–1). Pharmacodynamics governs the concentration-effect part of the interaction, whereas pharmacokinetics deals with the dose-concentration part (Holford et al, 1981). The pharmacokinetic processes of absorption, distribution, and elimination determine how rapidly and for how long the drug will appear at the target organ. The pharmacodynamic concepts of maximum response and sensitivity determine the magnitude of the effect at a particular concentration (see E_{max} and EC_{50}, Chapter 2).

Figure 3–1 illustrates a fundamental hypothesis of pharmacology, namely, that a relationship exists between a beneficial or toxic effect of a drug and the concentration of the drug. This hypothesis has been documented for many drugs, as indicated by the Effective Concentrations and Toxic Concentrations columns in Table 3–1. The apparent lack of such a relationship for some drugs does not weaken the basic hypothesis but points to the need to consider the time course of concentration at the actual site of pharmacologic effect (see below).

Knowing the relationship between drug concentration and effects allows the clinician to take into account the various pathologic and physiologic features of a particular patient that make him or her different from the average individual in responding to a drug. The importance of pharmacokinetics and pharmacodynamics in patient care thus rests upon the improvement in therapeutic benefit and reduction in toxicity that can be achieved by application of their principles.

PHARMACOKINETICS

The "standard" dose of a drug is based on trials in healthy volunteers and patients with average ability to absorb, distribute, and eliminate the drug (see Clinical Trials: The IND and NDA in Chapter 5). This dose will not be suitable for every patient. Several physiologic processes (eg, maturation of organ function in infants) and pathologic processes (eg, heart failure, renal failure) dictate dosage adjustment in individual patients. These processes modify specific pharmacokinetic parameters. The two basic parameters are **clearance,** the measure of the ability of the body to eliminate the drug; and **volume of distribution,** the measure of the apparent space in the body available to contain the drug. These parameters are illustrated schematically in Figure 3–2, where the volume of the compartments into which the drugs diffuse represents the volume of distribution and the size of the outflow "drain" in Figures 3–2B and 3–2D represents the clearance.

Volume of Distribution

Volume of distribution (V_d) relates the amount of drug in the body to the concentration of drug (C) in blood or plasma:

$$V_d = \frac{\text{Amount of drug in body}}{C} \qquad (1)$$